compared with cisplatin alone for mesothelioma improves survival,[30] we are currently studying a combination regimen using this alternative. A phase I trial of HIOC with cisplatin at its established MTD in combination with dose-escalated gemcitabine after EPP or P/D, as appropriate, is currently open at our institution (http://www.clinicaltrials.gov/ct2/results?term=tilleman). We are using gemcitabine combined with cisplatin rather than pemetrexed initially because it has been safely provided as intracavitary therapy in the abdomen for ovarian cancer.

The present prospective phase II study establishes that HIOC after EPP can be performed with acceptable morbidity and mortality compared with previous studies that report similar numbers.[7,25,26] Cytoprotection with amifostine and sodium thiosulfate merits further investigation for control of cisplatin-related renal toxicity.

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Discussion

Dr Valerie W. Rusch *(New York, NY)*. Thank you for asking me to discuss this excellent article, which was extremely well presented.

During the past 20 years, there have been significant improvements in the management of this disease, including a better understanding of its biology, improved methods and staging, decreases in operative mortality, and the development of better radiation and chemotherapy treatments. However, MPM is still refractory to standard treatment approaches and is usually fatal. Therefore novel approaches to the treatment of this disease are clearly needed, and in this regard I congratulate your group for innovative work testing the application of hyperthermic intracavitary chemotherapy to patients undergoing resection for MPM.

Intracavitary chemotherapy in conjunction with maximal cytoreductive surgery has become a standard treatment option for peritoneal-based malignancies, such as metastatic ovarian cancer and primary peritoneal mesothelioma. The mortality and morbidity of this treatment strategy are clearly linked to the expertise of the

surgical and anesthetic team because the operations are usually long and associated with high need for intravenous fluids and transfusions. Previous studies for peritoneal disease have shown that nonplatinum chemotherapy regimens appear to be associated with fewer serious adverse events, such as renal toxicity. Because intracavitary chemotherapy in either the pleural or peritoneal cavities penetrates to a depth of only about 5 mm, successful treatment with this modality depends on the amount of tumor remaining after cytoreductive surgery. Moreover, multiple cycles of intraperitoneal chemotherapy or the addition of systemic therapy appear to play a role in achieving better long-term disease control.

Other studies have tested the application of intracavitary chemotherapy to malignant pleural effusions and to metastatic thymoma. In the early 1990s at Sloan–Kettering, we performed a phase II trial in patients with MPM who received intrapleural cisplatin and mitomycin without hyperthermia immediately after pleurectomy and decortication. Systemic chemotherapy was added postoperatively. Briefly, this trial showed that intrapleural chemotherapy can be administered safely by using standard measures of intensive hydration without renal protective agents but that the treatment approach was relatively ineffective in preventing local tumor recurrence. Importantly, pharmacokinetic studies from that trial showed that very high chemotherapy drug levels can be achieved intrapleurally but that systemic absorption was rapid, with peak plasma levels being reached within 1 hour, emphasizing the importance of protecting renal function when administering cisplatin intrapleurally.

The present study by the Brigham group and the 2 previous trials that they performed extend this experience with intrapleural chemotherapy in several ways: by adding hyperthermia, which is thought to enhance chemotherapy activity; by adding sodium thiosulfate and amifostine as renal protective agents to enable the use of very high-dose chemotherapy; and by perfusing both the pleural and peritoneal cavities in the hope of decreasing the risk of peritoneal, as well as pleural, disease recurrence.

As shown here, the combined modality treatment was feasible with a 4% in-hospital mortality but was associated with significant morbidity. In the manuscript draft that I received, there was an overall 14% risk of significant renal dysfunction and a 13% risk of deep venous thrombosis and pulmonary embolus, a problem that has also been noted with intraperitoneal chemotherapy.

Unfortunately, the median survivals are very similar to those observed in trials of other, simpler treatment strategies, such as resection and radiation, and appear less favorable than the median survivals in recently reported European and North American trials of induction systemic therapy followed by EPP and adjuvant hemithoracic radiation. Moreover, recurrence in the ipsilateral thorax and peritoneum with this approach remains quite frequent.

Therefore at this point, one could ask whether the treatment strategy used in this trial is ready for export into more routine clinical practice. I think the answer is no, given the substantial risk of treatment-related morbidity and mortality and median survivals that do not suggest superiority over other treatment regimens. However, I hope that these provocative results will lead the Brigham group and other investigators to additional trials that will define the ultimate role of this approach in the treatment of this difficult disease. I would encourage them to consider pharmacokinetic studies that might identify ways to minimize renal toxicity. In this regard I would like to ask you 3 questions.

First, does the reduction of operative mortality from 11% in the first study reported by your group in the *Journal of Clinical Oncology* in which patients underwent pleurectomy and decortication to 4% in this trial that used EPP merely reflect a 10-year difference in the patients' median age between those 2 studies, or is it related to other factors?

Dr Tilleman. Dr Rusch, thank you very much for the summary and the review comments.

There is a difference between those 2 studies, the one reported in the *Journal of Clinical Oncology* and the one we are presenting right now. The difference can be attributed to several things. One of them is, as you pointed out, the difference in patient age (71 years for the P/D strategy vs 60 years for the current EPP strategy). I would like to emphasize that in the *Journal of Clinical Oncology* we have reported P/D in patients who were not eligible for EPP because of high risk; hence a higher mortality might be expected. The last contribution might be due to an improvement in the perioperative critical care during the years, and there is a learning curve here.

Dr Rusch. In a previous phase I trial you found that amifostine did not provide adequate protection against renal toxicity. Can you explain why it was added to thiosulfate in this study and why it appears that it might work?

Dr Tilleman. You are correct, the phase I study in which we applied only amifostine did not show significant renal protection; however, in this study we have shown that thiosulfate and amifostine administered together have created this change. In this study there were 9 patients who had renal toxicities with thiosulfate, and only a single patient had renal toxicity after the administration of amifostine in addition to thiosulfate. Therefore there might be a synergistic cytoprotective reaction, but as you quoted, amifostine alone did not provide such renal protection.

Dr Rusch. I will close with a third question. Given the frequency of intra-abdominal recurrence in this study and the well-known risk of tumor implantation by mesothelioma, have you reconsidered your strategy of perfusing both the chest and the abdomen?

Dr Tilleman. We reported in 1997 local recurrence within the ipsilateral hemithorax and by direct extension into the abdomen.[14] Adding intraoperative intracavitary chemotherapy reduced local recurrences from 67% to 34%, yet the abdominal recurrences did not change, even after adding intracavitary chemotherapy (Table 4).

Baldini and coworkers' work[14] showed the same abdominal recurrence rate (50% recurrence). Therefore, yes, a more rigorous treatment might be needed, including washing first the abdomen, omentectomy, and administration of systemic chemotherapy. All might reduce recurrences in the abdomen.